Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER P50973
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 10/030717
INTERNATIONAL APPLICATION NO. PCT/US00/21394	INTERNATIONAL FILING DATE 4 August 2000	PRIORITY DATE CLAIMED 6 August 1999
TITLE OF INVENTION PROCESS FOR PREPARING ACIDS VIA ALPHA-CHLOROEPOXY ESTERS		
APPLICANT(S) FOR DO/EO/US Ann M. DIEDERICH, Vance J. NOVAK		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [x] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [x] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [x] A FIRST preliminary amendment.

14. [ ] A SECOND or SUBSEQUENT preliminary amendment.

15. [x] Please amend the specification by inserting before the first line the sentence: This is a §371 national stage entry of International Application PCT/US00/21394, filed 4 August 2000, which claims benefit from the following Provisional Application: 60/147,576 filed 6 August 1999.

16. [ ] A substitute specification.

17. [ ] A change of power of attorney and/or address letter.

18. [x] An Abstract on a separate sheet of paper.

19. [ ] Other items or information:

JC13 Rec'd PCT/PTO 10 JAN 2002

US APPLICATION NO. (if known see 37 CFR 1.50) 10/030717	INTERNATIONAL APPLICATION NO. PCT/US00/21394	ATTORNEYS DOCKET NO. P50973	

20. [X] The following fees are submitted:				CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):					
Search Report has been prepared by the EPO or JPO **$890.00**					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) **$710.00**				**$710.00**	
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**					
Neither International Preliminary Examination Fee (37 CFR 1.492) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO............**$1,040.00**					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) and all claims satisfied provisions of PCT Article 33(2)-(4)..................**$100.00**					
ENTER APPROPRIATE BASIC FEE AMOUNT =				**$710.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				**$0.00**	
Claims	Number Filed	Number Extra	Rate		
Total claims	**19 - 20 =**	**0**	**0** x **$18.00**	**$0.00**	
Independent claims	**6 - 3 =**	**3**	**3** x **$84.00**	**$252.00**	
Multiple dependent claims (if applicable)			**+ $280.00**	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$962.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
SUBTOTAL =				**$962.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				**$**	
TOTAL NATIONAL FEE =				**$962.00**	
				Amount to be refunded	$
				charged	**$962.00**

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$962.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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EXPRESS MAIL CERTIFICATE: EV000523020US
DATE OF MAILING: 10 January 2002

PATENT
ATTORNEY'S DOCKET NUMBER **P50973**

TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE
(DO/US) - ENTRY INTO NATIONAL STAGE UNDER 35 USC 371

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/21394	**4 August 2000**	**6 August 1999**

TITLE OF INVENTION
Process for Preparing Acids Via Alpha-Chloroepoxy Ester

APPLICANT(S) FOR DO/US
Ann M. DIEDERICH, Vance J. NOVAK

Box PCT
Commissioner of Patents and Trademarks
Washington, D.C. 20231
ATTENTION: DO/US

PRELIMINARY AMEMDMENT

Dear Sir:

Preliminary to calculation of the filing fees and examination of the above noted application, entrance of the following remarks and amendments into the record is respectfully requested.

In the Claims:

Please amend the following claims:

7. The process of claim 2 wherein at 10-fold excess of dimethyl sulfoxide is used, the salt is sodium chloride and the reaction is heated to about 150 °C for about 3.5 hours.

12. The process of claims 8 wherein, in the compound of formula B, W is a bond and R' is CN or W is -C≡C-, R_1 is cyclopentyl and R_2 is CH_3.

REMARKS

This Preliminary Amendment is being made upon entry of International Application No. PCT/US00/21394 in the U.S. §371 national phase of prosecution.

A marked version of the amended claims accompanies this paper.

An abstract on a separate sheet of paper accompanies this request.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

James M. Kanagy
Attorney for Applicant
Registration No. 29,550

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MARKED UP VERSION OF CLAIMS TO SHOW CHANGES MADE

4. The process of any one of claims 1 wherein n in R_n is 2 and one group is substituted on at the 3 position and the other group is substituted on the 4 position.

5. The process of any one of claims 1 wherein R_1 is methyl, one of R_n is methoxy, -O-CF_3, -O-CHF_2, or -O-CH_2CHF_2 and the other is C_{4-6}cycloalkyloxy.

7. The process of claim 2~~, 3, 4, 5, or 6~~ wherein at 10-fold excess of dimethyl sulfoxide is used, the salt is sodium chloride and the reaction is heated to about 150 °C for about 3.5 hours.

12. The process of claims 8~~, 9, 10, and 11~~ wherein, in the compound of formula B, W is a bond and R' is CN or W is -C≡C-, R_1 is cyclopentyl and R_2 is CH_3.

ABSTRACT

This invention relates to a method for preparing certain acids of formula (I) via a chloroepoxy ester, which are useful as phosphodiesterase 4 inhibitors.

Process for Preparing Acids via Alpha-Chloroepoxy Esters

Area of the Invention

This invention relates to a method for preparing certain acids which are useful as phosphodiesterase 4 inhibitors. More specifically this invention relates to a method for converting cyclohexanones to cyclohexanoic acids via an alpha-haloepoxy ester.

Background of the Invention

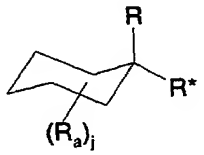
The process of this invention relates to making compounds which are useful in treating diseases modulated by the isoforms of the phosphodiesterase 4 enzyme. The alpha-haloepoxy esters used in this process are unique compounds and useful in making acids which are known PDE 4 inhibitors which are useful, among other things, for treating pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and asthma.

The compounds which are prepared by the methods of this invention and the intermediates disclosed herein are disclosed and described in the likes of U.S. patent 5,554,238 issued 03 September, 1996. That patent is incorporated herin by reference in full. Those compounds, particularly the 4-cyanocyclohexanoic acids, have marked effects on neutrophil activity, inhibiting neutrophil chemotaxis and degranulation *in vitro*. In animal models, those compounds reduce neutrophil extravasation from the circulation, pulmonary sequestration and the edematous responses to a number of inflammatory insults *in vivo*. They have been found to be useful in treating COPD in humans, and possibly in other mammalian species which suffer from COPD.

Herein there is provided a method for preparing certain of the phenyl-substituted cyclohexanoic acids, particularly those disclosed in US patent 5,554,238 by starting with a cyclohexan-1-one and proceeding via a novel intermediate, an alpha-haloepoxy ester, to the acid analog of the ketone starting material.

Summary of the Invention

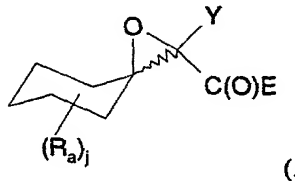
In a first aspect this invention relates to a process for preparing substituted cyclohexanoic acids of formula (I)



where R_a is a carbon-containing group optionally linked by oxygen, sulfur or nitrogen to the cyclohexyl ring and j is 1-10; and

R and R* are independently but not simultaneously hydrogen or C(O)E where E is OR_{14} or SR_{14};

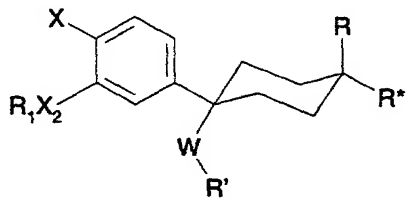
which process comprises treating an epoxide of formula A with dimethyl sulfoxide and an alkali metal salt wherein formula A is:



(A)

wherein E is OR_{14} or SR_{14} where R_{14} is hydrogen or alkyl of 1-6 carbon atoms; R_a is the same as defined for Formula (I); and Y is Br, Cl, F or I.

More particularly this invention relates to a process for preparing compounds of formula IA



(IA)

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties are unsubstituted or substituted with one or more halogens;

m is 0 to 2;

n is 0 to 4;

r is 0 to 6;

R_4 and R_5 are independently selected hydrogen or C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl or heterocyclic moiety is unsubstituted or substituted by 1 to 3 methyl groups, one ethyl group, or an hydroxyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl,or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2;

Y is O;

X_2 is O;

R_2 is $-CH_3$ or $-CH_2CH_3$, optionally substituted by 1 or more halogens;

R and R* are hydrogen or C(O)E wherein one of R or R* is always hydrogen and the other is always C(O)E where E is OR_{14}, or SR_{14};

W is a bond or is alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms;

when W is a bond R' is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, CN, OR_8, CH_2OR_8, NR_8R_{10}, $CH_2NR_8R_{10}$, C(Z')H, $C(O)OR_8$, or $C(O)NR_8R_{10}$; and

when W is alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms then R' is $COOR_{14}$, $C(O)NR_4R_{14}$ or R_7;

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is unsubstituted or substituted one or more times by: methyl or ethyl unsubstituted or substituted by 1-3 fluorines, or -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-CO_2R_8$, $-O(CH_2)_{2-4}OR_8$, $-O(CH_2)_qR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-O(CH_2)_qC(O)NR_{10}R_{11}$, $-O(CH_2)_qC(O)R_9$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_mR_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, or R_{13};

q is 0, 1, or 2;

R_{12} is R_{13}, C_3-C_7 cycloalkyl, or an unsubstituted or substituted aryl or heteroaryl group selected from the group consisting of (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), quinolinyl, naphthyl, and phenyl;

R_8 is independently selected from hydrogen or R_9;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

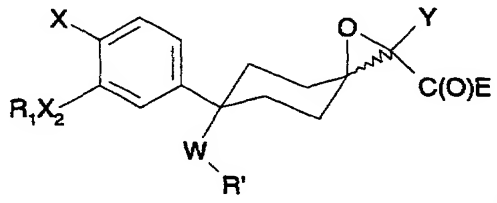
R_{10} is OR_8 or R_{11};

R_{11} is hydrogen, or C_{1-4} alkyl unsubstituted or substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S;

R_{13} is a substituted or unsubstituted heteroaryl group selected from the group consisting of oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, and thiadiazolyl, and where R_{13} is substituted on R_{12} or R_{13} the rings are connected through a carbon atom and each second R_{13} ring may be unsubstituted or substituted by one or two C_{1-2} alkyl groups unsubstituted or substituted on the methyl with 1 to 3 fluoro atoms; and

R_{14} is hydrogen or C_{1-6} alkyl;

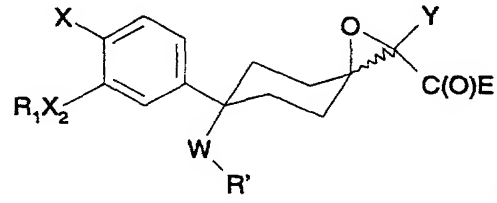
which process comprises treating an epoxide of formula A with dimethyl sulfoxide and an alkali metal salt wherein formula A is:



(A)

wherein X; R_1X_2; W; E; R'; and R_{14} are the same as defined for Formula (IA); and Y is Br, Cl, F or I.

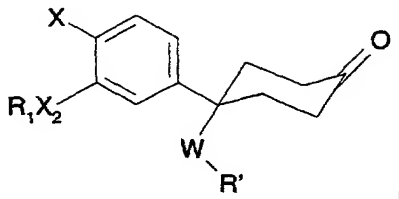
In a second aspect this invention relates to a process for making the epoxide of Formula (A)



(A)

where R_1X_2, X, W, R' and Y are the same as for Formula (IA) and the R_{14} in E is C_{1-6}alkyl; which process comprises treating a ketone of Formula (B) with an alkyldihaloacetate

or alkyldihalothioacetate in a polar aprotic solvent and optionally saponifying the resulting epoxy ester or thioester,



(B)

wherein X, R_1X_2, W and R' are the same as in Formula (A).

In a further aspect, this invention relates to a method for enriching the *cis* form of Formula (I) or (IA) where one of R or R* is C(O)OH or C(O)SH and the other is hydrogen in a mixture of *cis* and *trans* isomers. The method comprises esterifying the acid or thioacid or converting them to a mixed anhydride, if they are not already in that form, then treating the ester, etc, with an alkoxide base for a time sufficient to give a ratio of *cis* to *trans* isomers which is at least 4:1, perferably 7:1 or greater.

In yet another aspect, this invention relates to the haloepoxy acids and haloepoxy esters, thioesters and mixed anhydrides of formula A.

Detailed Description of the Invention

This invention provides a means for preparing cyclohexanoic acids. In particular it relates to a method for preparing cyclohexanoic acids which are phosphodiesterase 4 inhibitors as more fully disclosed in U.S. patent 5,554,238. The invention can also be used to prepare any cyclohexanoic acid and for enriching the *cis* form of a cyclohexanoic acid in a mixture of *cis* and *trans* isomers.

As regards the preferred substituents on Formulas (IA), (A) and (B), for R_1 they are CH_2-cyclopropyl or C_{4-6} cycloalkyl. Preferred R_2 groups are a C_{1-2} alkyl unsubstituted or substituted by 1 or more halogens. The halogen atoms are preferably fluorine and chlorine, more preferably fluorine. More preferred R_2 groups are those wherein R_2 is methyl, or a fluoro-substituted alkyl group, specifically a C_{1-2} alkyl such as a $-CF_3$, $-CHF_2$, or $-CH_2CHF_2$. Most preferred are the $-CHF_2$ and $-CH_3$ moieties. Most preferred are those compounds wherein R_1 is $-CH_2$-cyclopropyl, cyclopentyl, 3-hydroxycyclopentyl, methyl or CHF_2 and R_2 is CF_2H or CH_3. Preferably the R_{14} group will be methyl, ethyl or hydrogen. In formula (IA), methyl is the most preferred R_{14} group, and in Formula (I), it is methyl or hydrogen. Particularly preferred are those compounds where R_1 is cyclopentyl and R_2 is CH_3.

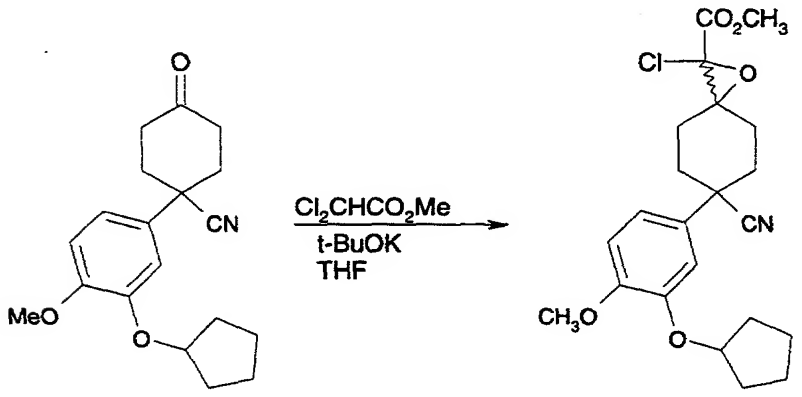
As regards W, the preferred embodiment is where W is a bond, ethylenyl, or -C≡C-. When W is a bond, the preferred R' group is CN. And when W is ethylenyl, -C≡C- the preferred R' group is hydrogen.

The most preferred compound of Formula (IA) made by the process of this invention is *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid].

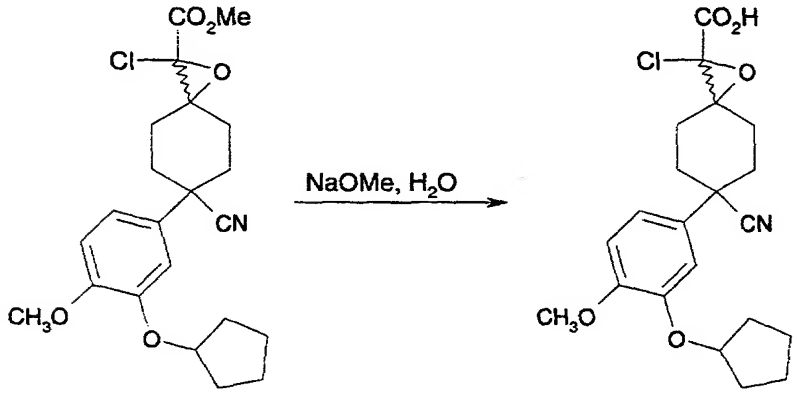
In regards to the epoxides, the lower alkyl chloroepoxy esters, thioesters and their corresponding acids are preferred. Methyl and ethyl are the most preferred ester-forming groups. The most perferred epoxides are methyl 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylate and 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylic acid.

Scheme I illustrates the conversion of a ketone of Formula (B) to the ester or acid of Formula (IA).

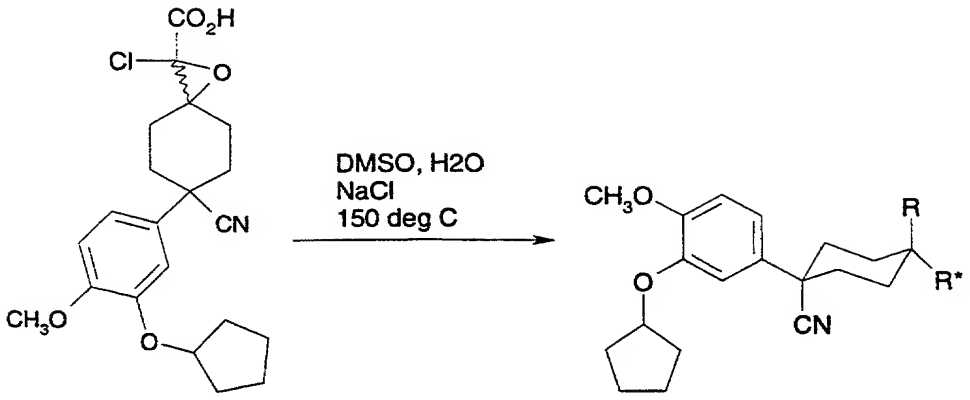
Scheme 1



(1-1) (1-2)



(1-2) (1-3)



(1-3) (1-4)

In compound 1-4, R and R* are hydrogen or C(O)OH, but R and R* are not both hydrogen or C(O)OH simultaneously.

The ketone starting material (1-1) can be prepared by the methods set out in U.S. patent 5,554,238 or 5,449,686. Forming the epoxide (1-2) is accomplished by treating the ketone with 1.1 to 2 equivalents of a lower alkyldihaloacetate using a polar non-protic solvent. "Lower alkyl" here means an alkyl radical having 1-6 carbon atoms. It is preferred to use about 1.5 equivalents of the acetate, and teterahydrofuran as the solvent. First the ketone (1-1) and the actetate are dissolved in the solvent. This solution is cooled to between -10 and +10 °C and an organic base is added in a molar excess (e.g. 1.1 to 2 equivalents, preferably about 1.5 equivalents). Herein an alkali metal *t*-butoxide is the preferred base, particularly potassium tert-butoxide. The temperature is kept at within the -10 to +10 °C range during the addition of the base and for some short period, 10 minutes to 45 minute thereafter. Product (1-2) is recovered by conventional means.

The ester (1-2) is then saponified using a base. This can be accomplished by any number of bases using conventional techniques. Herein this reaction is effected by treating the α-chloroepoxyester with sodium methoxide using a low molecular-weight alcohol and water as the solvent. A substantial molar excess of the base and solvent is used. For example a 5-fold excess of the base can be used and about a 10-fold excess of water. The ester is charged to a reaction vessel, dissolved in the alcohol, base is added and then the water is added The reaction goes to completion rapidly at room temperature, about 5 to 30 minutes. Product, the acid, is recovered by conventional means. Since it, the α-chloroepoxy acid (1-3), is relatively unstable it is preferred to immediately treat the epoxide with a reactant which opens the ring to give the acid.

Herein the epoxy acid (1-3) is rearranged to give 1-4 using dimethyl sulfoxide and an alkali metal salt. Water is used as a co-solvent. The alkali metal salt may be LiCl, KCl

or NaCl, or the corresponding flouride and bromide salts LiF, KF, NaF, LiBr, KBr, and NaBr. By way of more specific example, the chloroepoxy acid is dissolved in dimethyl sulfoxide and water and a small amount of a sodium chloride is added to the reaction pot which is then heated for several hours. A preferred set of reactants and conditions is one where about a 10-fold excess of DMSO (by weight/volume) is used to dissolve the acid and a small amount of water and a salt such as sodium chloride is added. This solution is heated to between about 125 and 175 °C for 2-5 hours; preferably the solution is heated to about 150 °C for 3.5 hours or so. This reaction gives the cyclohexanoic acid as a mixture of the *cis* and *trans* isomers in about a 1-1 ratio.

Enrichment of the *cis* isomer in the mixture of *cis* and *trans* isomers obtained from the just-described reaction is accomplished by activating it by, for example, forming an ester or mixed anhydride, and then treating the ester with an alkoxide base. This technique can be applied with satisfactory results to any preparation where one has a mixture of isomers and wishes to enrich the *cis* form of the isomer in that mixture. By way of example, the technique used here is to esterify the acid using an acid and a lower alkanol to form the ester of the alkanol. Methanol is most perferred. This mixture is then treated with *t*-butanol and its alkali metal salt for an extended period, for between 5 and 24 hours for example; a preferred time is about 12 hours. This latter step results in an enrichment of the *cis* form of the product; the equilibration process gives the preferred *cis* form of the acid.

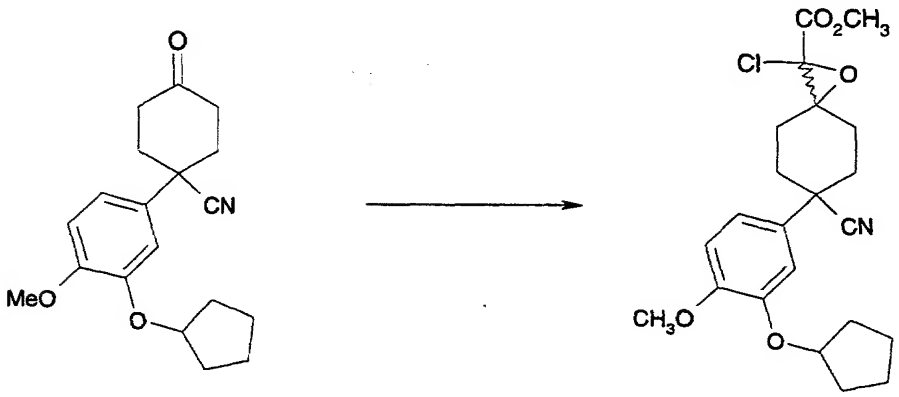
An alternative process is to combine the step of opening of the epoxy acid, really a decarboxylation, with the esterification step by using a lower alkanol or lower thioalkanol (1-6 carbons) as the co-solvent instead of water. The re-equilibration can be effected by adding the appropriate alcohol and its alkali metal salt to the reaction flask once the ester has been formed from the α-haloepoxy acid without isolating the ester. For example methanol rather than water can be used as the solvent for the dimethyl sulfoxide/salt reaction. If this is done, one obtains the methyl ester as the product, rather than the acid obtained when water is used as the solvent. However if methanol or another low boiling-point alkanol is used, a pressurizable reaction vessel must be employed since the solution must be heated to about 150 °C to effect the decarboxylation, at which temperature the methanol would be mostly vaporized if the reaction was run at 1 atmosphere of pressure. A preferred approach is to run the reaction using methanol in a pressurized container, cooling the reaction mixture to about room temperature, and adding the likes of *t*-butanol and its alkali metal salt to effect the coversion of the *trans* form to the *cis* isomer.

By way of further illustration, but without intending to be limited in any way, the following illustrative examples are provided.

Examples

Example 1

Preparation of methyl 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylate

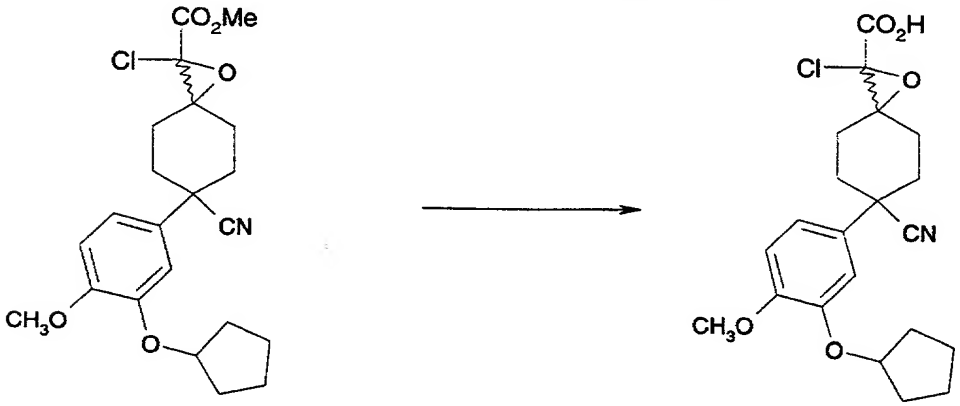


(1) (2)

A 100 mL round-bottom flask was charged with 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one (1)(4.0 g, 12.8 mmole, 1.0 eq), methyldichloroacetate (2.74 g, 1.98 mL, 19.1 mmole, 1.5 eq), and tetrahydrofuran (THF, 40 mL). The solution was cooled to 0 °C in an ice bath, then potassium tert-butoxide was added (19.1 mL, 19.1 mmole of a 1M solution in THF) while maintaining the temperature below 5 °C (about 25 minutes). The reaction was deemed complete at the end by TLC (hexanes/ethyl acetate @3/1, silica gel plates), then was poured into ethyl acetate and 5% HCl for an extractive workup. The layers were separated and the water layer was extracted with ethyl acetate twice. The combined ethyl acetate layers were extracted with 5% sodium bicarbonate and with brine. The ethyl acetate layer was concentrated under vacuum to a yellow oil. The oil was dissolved in 3/1 hexanes/ethyl acetate and filtered through 1.5 " of flash silica gel. Concentration produced the product methyl 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylate as a clear, colorless oil. The molecular weight and structure of the product was confirmed to be the methyl α-chloroepoxy ester by mass spec.

Example 2

Preparation of 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylic acid

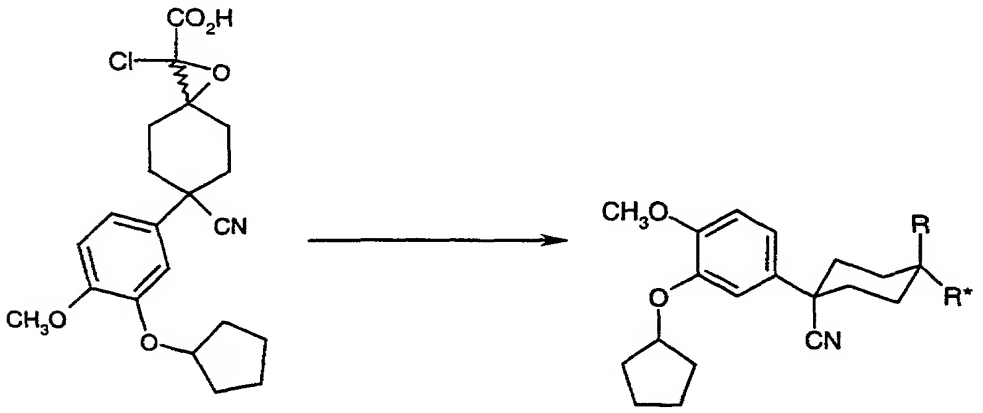


(2) (3)

A 50 mL flask was charged with the chloroepoxyester (2) (3.0 g, 4.77 mmole), 30 mL of methanol, sodium methoxide (5.16 g of 25 wt % solution in methanol, 23.9 mmole) and water (0.8 g, 44 mmole). The solution was stirred for 10 minutes and the reaction was deemed complete by TLC (hexanes/ethyl acetate @3/1, silica gel plates). The reaction was poured into an addition funnel containing 100 mL of 1% HCl and 100 mL of *t*-butylmethyl ether. The organic layer was extracted once with water and once with brine, then was concentrated to an oil under reduced pressure. The product 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylic acid was confirmed by mass spectral analysis.

Example 3

Preparation of *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]



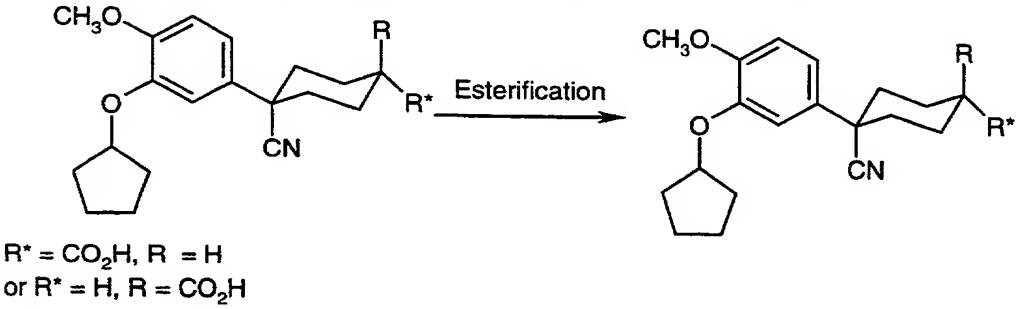
(3) (I)

In this example, either R or R* can be C(O)OH; the other group must be hydrogen.

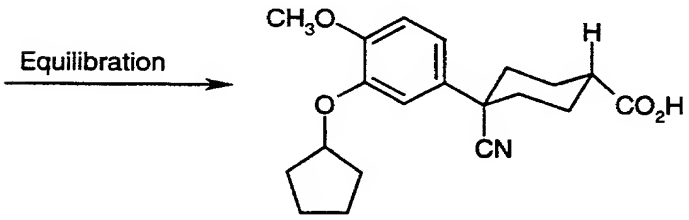
Freshly prepared chloroepoxyacid (3) (2.79 mmole) was treated with dimethyl sulfoxide (7.5 mL), water (0.5 mL), and NaCl (50 mg). The solution was heated to 150 °C for 3.5 hours. The reaction was followed by HPLC (15 cm Supelcocil, ACN/water/TFA [40/60/0.1] 1.5 mL/min,215 nm UV, *trans* form -- at 10.6 min and *cis* form at 11.3 min). The yield was calculated using weighted assay. The yield was 59% for the two isomers in a ratio of one-to-one.

Example 4

Enrichment of the *Cis* Isomer in a *Cis/Trans* Mixture of [4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]



R* = CO_2H, R = H
or R* = H, R = CO_2H



cis form

The isomeric mixture obtained in the previous step was dissolved in 10 mL of methanol. *p*-Toluenesulfonic acid (0.1 g) was added and the reaction was refluxed for 12 hours to form the methyl esters. The reaction was diluted with ethyl acetate and water. The layers were separated, then the organic layer was concentrated. The oil was dissolved in about 10 mL of tBuOH and then 7.5 mL of potassium *t*-butoxide (1M in t-BuOH) was added for the equilibration. After stirring overnight, a small sample was treated with water and the ratio of cis to trans isomers of [4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] was calculated as 9.6/1 by HPLC (15 cm Supelcocil, ACN/water/TFA [40/60/0.1] 1.5 mL/min,215 nm UV, *trans* form at 10.6 min and *cis* form at 11.3 min). The reaction was quenched by adding 1% HCl and ethyl acetate to extract. The layers were separated and the organic layer was extracted once with water. The product layer was concentrated and then treated with ethyl acetate. The product was precipitated by adding about one volume of hexanes. No *trans* form was detected in the product.

This reaction was also run using NaH under the same conditions. It gave an 8:1 ratio of *cis*:*trans* isomers. When the same reaction was run using NaH in ethanol (methyl

ester) a 7:1 ratio was obtained. Using the ethyl ester rather than the methyl ester as the substrate, and NaH and ethanol, a 10:1 ratio was obtained.

Example 5

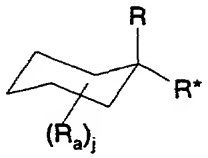
One-Pot Preparation of the *Cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] from Methyl 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylate

Chloroepoxyester (0.72 g purified, 1.71 mmole) in methanol (5 mL) was treated with sodium methoxide (1.42 g of 25% wt solution in methanol, 6.5 mmole) and water (0.5 mL) and stirred for 15 minutes. The reaction was quenched with *t*-butylmethyl ether and 1% HCl. The bottom layer was removed, then the organic layer was washed three times with water. The organic layer was concentrated under reduced pressure, then the water was azeotroped by adding methanol and reconcentrating.

Dimethylsulfoxide (7 mL), sodium chloride (0.5 g) and methanol (5 mL) were added. The contents were then heated under pressure to 150 °C for 1.5 hours. The HPLC (15 cm Supelcocil, ACN/water/TFA [40/60/0.1] 1.5 mL/min,215 nm UV) showed the isomeric mixture of esters and acids at 10.5/1 (esters/acids). The reaction was cooled, then 10 mL of t-BuOH and 0.20 g of t-BuOK was added The solution was stirred overnight to give a 7/1 ratio of *cis/trans* isomers. The reaction was worked up with 1% HCl and t-butylmethyl ether. The layers were separated and the organic layer was concentrated to an oil. The oil was dissolved in a minimum amount of warm ethyl acetate, and the product was precipitated by adding hexanes, cooled to 0 °C, then filtered. The product was a light tan solid; no trans isomer was detected.

What is claimed is:

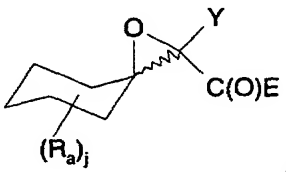
1. A process for preparing substituted cyclohexanoic acids of formula (I)



where R_a is a carbon-containing group optionally linked by oxygen, sulfur or nitrogen to the cyclohexyl ring and j is 1-10; and

R and R* are independently but not simultaneously hydrogen or C(O)E where E is OR_{14} or SR_{14} where R_{14} is hydrogen or alkyl of 1-6 carbon atoms;

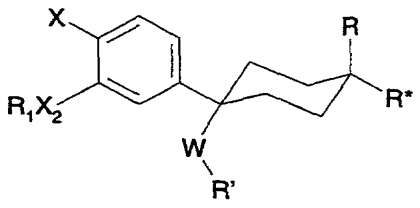
which process comprises treating an epoxide of Formula A with dimethyl sulfoxide and an alkali metal salt, wherein Formula A is:



(A)

wherein E is OR_{14} or SR_{14} where R_{14} is hydrogen or alkyl of 1-6 carbon atoms; R_a is the same as defined for Formula (I); and Y is Br, Cl, F or I.

2. A process for preparing compounds of formula IA



(IA)

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties are unsubstituted or substituted with one or more halogens;

m is 0 to 2;

n is 0 to 4;

r is 0 to 6;

R_4 and R_5 are independently selected hydrogen or C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl or heterocyclic moiety is unsubstituted or substituted by 1 to 3 methyl groups, one ethyl group, or an hydroxyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl,or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2;

Y is O;

X_2 is O;

R_2 is $-CH_3$ or $-CH_2CH_3$, optionally substituted by 1 or more halogens;

R and R* are hydrogen or C(O)E wherein one of R or R* is always hydrogen and the other is always C(O)E where E is OR_{14}, or SR_{14};

W is a bond or is alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms;

when W is a bond R' is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, CN, OR_8, CH_2OR_8, NR_8R_{10}, $CH_2NR_8R_{10}$, C(Z')H, $C(O)OR_8$, or $C(O)NR_8R_{10}$; and

when W is alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms then R' is $COOR_{14}$, $C(O)NR_4R_{14}$ or R_7;

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is unsubstituted or substituted one or more times by: methyl or ethyl unsubstituted or substituted by 1-3 fluorines, -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-CO_2R_8$, $-O(CH_2)_{2-4}OR_8$, $-O(CH_2)_qR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-O(CH_2)_qC(O)NR_{10}R_{11}$, $-O(CH_2)_qC(O)R_9$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$,

$-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_mR_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, or R_{13};

q is 0, 1, or 2;

R_{12} is R_{13}, C_3-C_7 cycloalkyl, or an unsubstituted or substituted aryl or heteroaryl group selected from the group consisting of (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), quinolinyl, naphthyl, and phenyl;

R_8 is independently selected from hydrogen or R_9;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

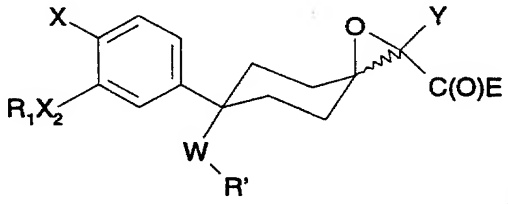
R_{10} is OR_8 or R_{11};

R_{11} is hydrogen, or C_{1-4} alkyl unsubstituted or substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S;

R_{13} is a substituted or unsubstituted heteroaryl group selected from the group consisting of oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, and thiadiazolyl, and where R_{13} is substituted on R_{12} or R_{13} the rings are connected through a carbon atom and each second R_{13} ring may be unsubstituted or substituted by one or two C_{1-2} alkyl groups unsubstituted or substituted on the methyl with 1 to 3 fluoro atoms; and

R_{14} is hydrogen or C_{1-6} alkyl;

which process comprises treating an epoxide of Formula A



(A)

with dimethyl sulfoxide and an alkali metal salt;

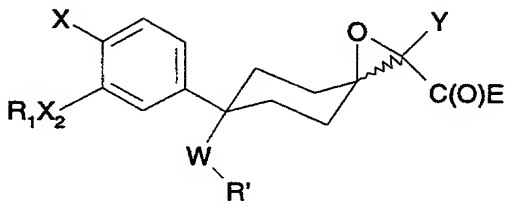
wherein X; R_1X_2; W; E; R'; R_{14} are the same as defined for Formula (IA); and Y is Br, Cl, F or I.

3. The process of claim 2 wherein alkali metal salt is LiCl, KCl, or NaCl and the reaction is carried out at between about 125-175 °C or 2-5 hours.

6. The process of claim 5 wherein, in the compound of formula A, W is a bond, R' is CN.

7. The process of claim 2, 3, 4, 5, or 6 wherein at 10-fold excess of dimethyl sulfoxide is used, the salt is sodium chloride and the reaction is heated to about 150 °C for about 3.5 hours.

8. A process for preparing an epoxide of Formula (A)



(A)

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties unsubstituted or substituted with one or more halogens;

m is 0 to 2;

n is 0 to 4;

r is 0 to 6;

R_4 and R_5 are independently selected hydrogen or C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl or heterocyclic moiety is unsubstituted or substituted by 1 to 3 methyl groups, one ethyl group, or an hydroxyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl,or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2;

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl,or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2;

Y is O;

X_2 is O;

W is a bond or is alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms;

when W is a bond, R' is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, CN, OR_8, CH_2OR_8, NR_8R_{10}, $CH_2NR_8R_{10}$, C(Z')H, $C(O)OR_8$, or $C(O)NR_8R_{10}$; and

when W is alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms, R' is R' is $COOR_{14}$, $C(O)NR_4R_{14}$ or R_7;

R_2 is $-CH_3$ or $-CH_2CH_3$, optionally substituted by 1 or more halogens; and

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is unsubstituted or substituted one or more times by: methyl or ethyl unsubstituted or substituted by 1-3 fluorines, -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-CO_2R_8$, $-O(CH_2)_{2-4}OR_8$, $-O(CH_2)_qR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-O(CH_2)_qC(O)NR_{10}R_{11}$, $-O(CH_2)_qC(O)R_9$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_{m'}R_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, or R_{13};

q is 0, 1, or 2;

R_{12} is R_{13}, C_3-C_7 cycloalkyl, or an unsubstituted or substituted aryl or heteroaryl group selected from the group consisting of (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), quinolinyl, naphthyl, and phenyl;

R_8 is independently selected from hydrogen or R_9;

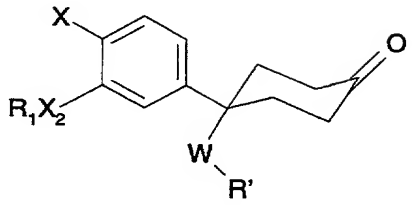
R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11};

R_{11} is hydrogen, or C_{1-4} alkyl unsubstituted or substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S;

which process comprises;

treating a ketone of Formula (B)



(B)

wherein X and R_1X_2 are the same as in Formula (A);

with a lower alkyldihaloacetate in a polar aprotic solvent, and

optionally saponifying the resulting alpha-haloepoxy ester.

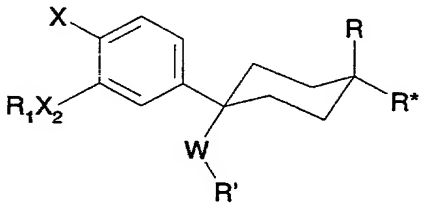
9. The process of claim 8 wherein, in the compound of formula B, R_1 is CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, or C_{4-6} cycloalkyl and R_2 is C_{1-2} alkyl unsubstituted or substituted by 1 or more halogens, the lower alkyldihaloacetate is lower alkyl dichloroacetate, and the base is an alkali metal *t*-butoxide.

10. The process of claim 9 wherein about 1.5 equivalent of the acetate and 1.5 equivalents of alkali metal *t*-butoxide are used.

11. The process of claim 10 wherein the acetate is methyl or ethyl dichloroacetate and the base is potassium *t*-butoxide.

12. The process of claims 8, 9, 10, and 11 wherein, in the compound of formula B, W is a bond and R' is CN or W is -C≡C-, R_1 is cyclopentyl and R_2 is CH_3.

13. A process for enriching the *cis* form of a compound of Formula (IA)



(IA)

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties unsubstituted or substituted with one or more halogens;

m is 0 to 2;

n is 0 to 4;

r is 0 to 6;

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties unsubstituted or substituted with one or more halogens;

m is 0 to 2;

n is 0 to 4;

r is 0 to 6;

R_4 and R_5 are independently selected hydrogen or C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl or heterocyclic moiety is unsubstituted or substituted by 1 to 3 methyl groups, one ethyl group, or an hydroxyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl,or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2;

Y is O;

X_2 is O;

R_2 is $-CH_3$ or $-CH_2CH_3$, optionally substituted by 1 or more halogens;

R and R* are hydrogen or C(O)E wherein one of R or R* is always hydrogen and the other is always C(O)E where E is OR_{14} or SR_{14} and R_{14} is hydrogen;

W is a bond or is alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms;

when W is a bond R' is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, CN, OR_8, CH_2OR_8, NR_8R_{10}, $CH_2NR_8R_{10}$, C(Z')H, $C(O)OR_8$, or $C(O)NR_8R_{10}$; and

when W is alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms then R' is R' is $COOR_{14}$, $C(O)NR_4R_{14}$ or R_7;

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is unsubstituted or substituted one or more times by: methyl or ethyl unsubstituted or substituted by 1-3 fluorines, -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-CO_2R_8$, $-O(CH_2)_{2-4}OR_8$, $-O(CH_2)_qR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-O(CH_2)_qC(O)NR_{10}R_{11}$, $-O(CH_2)_qC(O)R_9$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_mR_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, or R_{13};

q is 0, 1, or 2;

R_{12} is R_{13}, C_3-C_7 cycloalkyl, or an unsubstituted or substituted aryl or heteroaryl group selected from the group consisting of (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), quinolinyl, naphthyl, and phenyl;

R_8 is independently selected from hydrogen or R_9;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11};

R_{11} is hydrogen, or C_{1-4} alkyl unsubstituted or substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S;

R_{13} is a substituted or unsubstituted heteroaryl group selected from the group consisting of oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, and thiadiazolyl, and where R_{13} is substituted on R_{12} or R_{13} the rings are connected through a carbon atom and each second R_{13} ring may be unsubstituted or substituted by one or two C_{1-2} alkyl groups unsubstituted or substituted on the methyl with 1 to 3 fluoro atoms;

which process comprises treating the lower alkyl ester, lower alkyl thioester or mixed anhydride of Formula (IA) with an alkoxide base.

14. The process of claim 13 wherein the compound of formula IA, R_1 is CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, or C_{4-6} cycloalkyl, R_2 is C_{1-2} alkyl unsubstituted or substituted by 1 or more halogens, the base is a alkali metel t-butoxide, and the reaction runs for 5-24 hours.

15. The process of claim 13 wherein the compound of formula IA is [4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid].

16. The process of claim 13 wherein the base is potassium *t*-butoxide.

17. A compound which is lower alkyl 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylate.

18. The compound of claim 17 which is methyl 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylate.

19. A compound which is 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxaspiro[2.5]octane-2-carboxylic acid.

Docket No.: P50973

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: "**PROCESS FOR PREPARING ACIDS VIA ALPHA-CHLOROEPOXY ESTERS**"

the specification of which (check one)
[ ] is attached hereto.
[X] was filed on **04 August 2000** as Serial No. **PCT/US00/21394**
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
60/147,576	**06 August 1999**

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

Customer Number 20462.

Address all correspondence and telephone calls to **James M. Kanagy**, SmithKline Beecham Corporation, Corporate Intellectual Property-U.S., UW2220, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939, whose telephone number is 610-270-5014.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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